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Short Summary Version of Eric Jeffries Report

July 7, 2001

Eric Jeffries
2338 Bedford Ave.
Cincinnati, Ohio, 45208
USA

Dear Eric:

You have asked that I prepare an up-to-date, detailed report of my findings, analysis, and opinions regarding your illness. You have also asked that I prepare a summary of my full report and analysis. This document is the requested summary and the attached document is my full, up-to-date, and detailed report, which should be referenced for more detailed findings, analysis, and discussions. I understand that this will be shared with others. I have attached my Curriculum Vitae.

In my opinion the June 1997 Hepatitis A and B immunization Mr. Jeffries received, at a time when he was still ill with an existing infectious illness has caused Mr. Jeffries to suffer a downward spiral of his health which led to his permanent departure from work in September 1998. I have reviewed all of Mr. Jeffries' medical records and test results supplied in addition to conducting my own interviews, examinations, and tests. My treatment and observations of Mr. Jeffries began in June 2000 and continues through today. On the basis of all of this information, it is my opinion that:

(1) Mr. Jeffries has an evolving, ongoing immune mediated injury. The areas most injured appear to be to his Central Nervous System ("CNS"), specifically his brain. He has had also a significant autoimmune injury affecting his red blood cells and his thyroid gland, the injury to the thyroid gland resulted in Hashimoto's thyroiditis and malignancy of that gland, there also appears to be involvement of his testes;

(2) Mr. Jeffries' chronic illnesses started shortly after his June 1997 immunizations and gradually became increasingly disabling. He remains significantly disabled with major and minor variations but no periods of sustained recovery; and

(3) Mr. Jeffries' illness totally disables him from returning to his previous employment, or remunerative intellectual work of any kind. Furthermore, it is my opinion that his total disability has persisted from at least the time Mr. Jeffries ceased employment in September 1998, and will continue into the foreseeable future.

The Medical Evidence

The test results, symptoms, and pattern of Mr. Jeffries' illness are consistent with both autoimmune and CNS disease. His illness continues to progress in an intermittent, repetitive, and disabling fashion. In fact, the tests I performed and/or reviewed are more than sufficient to demonstrate major illnesses. Numerous objective and clinical abnormalities have surfaced during the course of the treatment of Mr. Jeffries' illness. Over a dozen observation areas and/or test results, on which I base my opinions and conclusions are set forth below:

1. Thyroid Cancer. I discovered a nodule on the right lobe of Mr. Jeffries' thyroid. Tests suggested a significant auto-immune attack on his thyroid gland and conversely, serious autoimmune disease. Further investigation uncovered the fact that Mr. Jeffries' thyroid was cancerous. The thyroid was also involved in an autoimmune inflammatory breakdown diagnosed as Hashimoto's Thyroiditis. The carcinoma, thyroid, and surrounding lymph nodes were removed. It is my opinion that this malignancy was a response to the immunization. In removing the malignant thyroid gland his physicians were obliged to remove two of his 4 parathyroid glands. The status of the remaining two parathyroid glands is not known.

2. Brain Scans. Mr. Jeffries had several abnormal brain scans (i.e., SPECT Scans, PET Scans, and MRI's) which appear to be the result of damage to either the microcapillary or small arteries to the brain cells or the brain cells themselves.

   A. First NeuroSPECT. SPECT scans demonstrate a patho-physiology of brain blood flow at a micro-arterial or capillary level and brain cell dysfunction. This first SPECT scan demonstrated significant modifications of brain physiology characterized by an irregular distribution in both middle cerebral artery regions and reduced uptake mostly in the cortical areas of the brain, the temporo-parietal lobe, and the subcortical areas of the brain, the posterior fossa and the pons. There is sometimes termed a vasculitis pattern and is consistent with an autoimmune reaction affecting the small blood vessels of the CNS. Mr. Jeffries may also have a similar pathology affecting all of the small blood vessels in the body or it may be localized to the CNS.

   B. Second NeuroSPECT. Mr. Jeffries' second SPECT scan demonstrated quite irregular cortical distribution of both middle cerebral arteries. The reduced uptake is most pronounced in the posterior temporo-parietal regions but in both left and right hemispheres. There is also reduced uptake in the posterior fossa, primarily in the cerebellum. This finding remains unchanged or worse than the first SPECTand consistent with the first NeuroSPECT scan.

   C. The Combined SPECT scans. Both SPECT scans showed consistent and pathological scans of both the cortex and subcortical areas of Mr. Jeffries' brain. It is clear, therefore, that Mr. Jeffries has an encephalopathy consistent with an autoimmune encephalopathy. This type of scan is sometimes referred to a vasculitis pattern and can be seen in patients with a vasculitis or an autoimmune reaction involving the fine cerebral arteries. These persisting abnormalities are consistent with a chronic form of

microvascular pathology. We see this type of pattern only in our most chronically ill patients.

Mr. Jeffries' brain scan is typical of the degree of pathology seen in HIV+/AIDS encephalopathy (but he is not HIV+ and does not have AIDS). However, as noted previously, Mr. Jeffries' immune system tests are grossly abnormal. In examination of the actual colour print-outs of the functional brain maps, one can observe the marked irregularities of the outside contours of the brain as well as that of the ventricles. The brain scans themselves demonstrate this lack of symmetry.

There also appears hypoperfusion in the posterior optical cortex in the sagital views (see views 7 & 8 and to a lesser extent in 9 in the 10:32 am views in the circulatory phase). There also appears to be a hypoperfusion in the area of the subcortical areas where the basal ganglia are located. This area again appears to be distorted. The basal ganglia represents only a small part of this hypoperfused area. The 12:26 pm views also demonstrate the markedly irregular vasculitis pattern noted in the10:32 am views. These views represent metabolic aspects of the brain cells and once again these views are pathological and represent an encephalopathic condition of his physiological brain architecture. The subcortical architecture is even more irregular and represents a greater degree of pathology than the abnormal cortex. In this patient both left and right sides of the brain appear dysfunctional. The area of the motor cortex, responsible for normal physical movement and response appears pathologically effected.

These anomalies alone would suggest that Mr. Jeffries has difficulties in interpretation of visual and auditory information. These findings are consistent with Mr. Jeffries complaints and difficulties noted since shortly after receiving the double immunization. In my opinion, these pathological anomalies are totally inconsistent with Mr. Jeffries previous ability to perform his occupation. His clumsiness, abnormal balance and walking ability, and his wide leg stance are echoed in the abnormal scans of both Mr. Jeffries' abnormal motor cortex and abnormal posterior subcortical brain, in addition to the cerebella patho-physiological features.

D. PET Scan. The results of Mr. Jeffries' Positron Emission Tomography tests (i.e., PET Scans) show clear metabolic decreases in the dorsolateral prefrontal cortex. There is metabolic decrease in the right temporal insular cortex. There is a pattern of metabolic hypofrontality with decreased frontal to occipital rations. This pattern of abnormalities is compatible with encephalopathy.

Incorporated into this report are three coloured PET Scan print-outs. (*See, Attached*). The first page represents a section cut relatively high in the brain, the second in the middle areas of the brain, and the third at a lower section. On each page the upper row of images represents a normal control brain, the second row Mr. Jeffries' brain findings, and the third row the subtraction of the second from the first image. You can readily observe how unusual Mr. Jeffries' brain appears in relationship to the first normal control brain images. In the third row the subtraction is demonstrated. On the fourth row we see

the Brodman area numbers so that you can refer back to specific brain areas by number and consult a Brodman guide in order to note the areas of dysfunction.

Mr. Jeffries' PET Scan shows multiple brain anomalies in widely dispersed cortical and subcortical areas. The changes in page 3, views 2 and 3 in the cerebellum are quite extensive and reinforce the fact that this patient has a significant movement disorder, which is clearly evident and confirmed in the insurance company's videotape of this patient. It is of significant concern that the changes are so widespread in both the thinking brain and equally in the subcortical or primitive brain that responds to balance, integration and reconstruction of information in the thinking or intellectual brain.

Although I describe these as changes or anomalies they are probably better described as injuries and are most unusual in a young man. The changes are likely due to the autoimmune effects of the Hepatititis B immunization given on top of an existing infection. They could be due to a wide spread micro-vascular injury such as a low grade infection that could also be due to the Hepatitis B immunizaton "eternalizing" an existing minor infection. Regardless, the changes are clearly pathological. For someone in his eighties this condition might be considered expected although unacceptable. However based on Mr. Jeffries' history and all of the significant numbers of immune and brain changes that I have catalogued, these changes must be considered to be grossly pathalogical.

E. MRI Brain Scan. Mr. Jeffries' MRI Brain Scan is abnormal in that there are non-specific areas of increased signal intensity in the subcortical white matter. These are seen in increased frequency in patients of this age who have the clinical stigmata of what is referred to chronic fatigue syndrome. It is judged that they are due to pathological fluid levels or inflammatory membrane linings of Virchow Robin spaces. It is my opinion that this test demonstrates that there are pathological spaces in Mr. Jeffries' periarterial areas that prevent the normal passage of oxygen and nutrients across the cell membrane and into the associated brain areas. In my experience, this phenomenon is seen most frequently in acute onset post infectious type illess.

3. Immune Tests: Mr. Jeffries' immune tests were significantly abnormal and consistently abnormal in immune distribution over a long period of time. These abnormalities were found by his US physicians and continue in our tests in Canada. The fact that more recent immune tests demonstrate greater abnormality may represent that Mr. Jeffries' immune status is gradually becoming worse. It is important and significant that this patient's tests are consistent and significantly depressed right across the immune spectrum examined. This may also suggest that the patient has an increased risk of falling ill with other infectious diseases and possibly further malignancies.

4. Immune globulin survey: These tests indicate that there is a significant immune anomaly in Mr. Jeffries' immune status and the probability that he has a significant immune dysfunction or disease. These tests are consistent with the other consistently grossly abnormal immune function tests. Accordingly, it is my opinion that Mr. Jeffries suffers from a significant immune dysfunction.

5. **General Appearance**. By his general appearance, Mr. Jeffries presents Parkinsonian-like faces, walks with a wide leg stance, and is in obvious discomfort. At times he limps. He was not able to keep up to me even when I walk slowly. He appears clumsy. He has an abnormal speech pattern with almost scanning speech. He does not talk normally. He gets lost in sentence and frequently cannot remember what he is saying. He had a contrary pupillar reflex and other minor eye reflex abnormalities that might be consistent with the abnormal SPECT findings. He also has several curious minor neurological abnormalities.

I reviewed a videotape taken over several days during the period of December 6th to January 8th by his insurance company or companies. This film is quite revealing in that at no time does he appear normal. He is obviously in pain in several of these episodes, he walks with a stiff limbed almost Frankenstein walk. Often he limps suggesting joint or back pain. His head is bowed over, his upper thoracic spine is humped or hunch backed and it is obvious that walking is difficult for him. His time reactions are always slow and often clumsy. When another adult or his children accompany him, the others move about at a regular speed and Mr. Jeffries is left far behind. At times he walks with a wide stanced walk. He looks and acts like a typical Parkinsonian brain dysfunction.

From these observations, it is clear that Mr. Jeffries has a definite motor problem and balance problem and probably a subcortical injury. He has a movement disorder but although this may be an early Parkinson's disease it is more likely a result of the subcortical and cortical vasculitis type and perfusion pathology seen on the SPECT scans. From the abnormal SPECT Scans I would suggest he has a significant CNS injury-giving rise to this movement disorder. Also, on all visits he has had a twitching movement of his fingers. This is a physical sign associated with CNS vasculitis.

6. **Blood Pressure Tests**. Although Mr. Jeffries' brachial pressures are normal to subnormal his pulse pressures are not normal. His falling pulse pressures may be indicative of dysautonomia. This can be suggestive of an injury to the brain in the area of the subcortex. Mr. Jeffries' pulse pressure falls significantly when he changes from a supine to sitting to a standing position. This is an abnormal finding. It may suggest an abnormal autonomic status in which the subcortical brain has lost its ability to create a normal pressure response in the extremities. Effectively, what this means is that as soon as Eric stands there is a decrease in blood pressure such that he may have insufficient blood to keep his brain supplied with adequate oxygen levels.

7. **Blood Volumes.** Mr. Jeffries test results show an abnormal pathological decrease in circulating red blood cell and plasma volumes. The red blood cell volumes available to carry oxygen to Mr. Jeffries' brain, muscles, and gut are in the range of 75% when sitting and possibly as low as 65 % when standing. This phenomenon combined with the falling pulse pressure would have a profound effect on his ability to deliver oxygen and insulin for adequate cell metabolism and would interfere with normal brain metabolism. This could certainly contribute in part to Mr. Jeffries' decreased intellectual and energy abilities. When this abnormality is coupled with the falling blood pressure that occurs when he is standing, the oxygen deprivation to his CNS may be even more exaggerated.

8. **Natural Killer Cells ("NKC").** NKC number tests performed on two separate occasions suggest that there is an over-activity of the NKC as well as an increased number. This could mean at least one or two of the following: (1) Mr. Jeffries has a malignancy that his body is attempting to destroy; and/or (2) Mr. Jeffries has an acute ongoing or chronic infection that his immune system is attempting to eradicate.

9. **Reticulocytes.** Mr. Jeffries' elevated reticulocyte level represents a pathological abnormality. An abnormal increase in reticulocytes is seen when an increase in red blood cell production is occurring as the bone marrow replaces cells lost or prematurely destroyed. It is suggestive of occult disease such as haemolytic aenemia. In Mr. Jeffries this suggests a pathological autoimmune destruction of the patient's red blood cells. Reticulocytosis can be seen in leukemia and lymphoma.

10. **Hepatitic panel:** Mr. Jeffries' abnormal test results are suggestive of a liver dysfunction, disease or inflammation. This could be viral, immunological, inflammatory, infectious, or secondary to immunization disease or a combination of any of the above.

11. **Bilirubin:** Shortly after receiving the combined Hepatitis A & B immunization, tests conducted revealed, among other things, abnormal and elevated bilirubin, elevated liver enzymes, and an enlarged tender liver. At the same time Mr. Jeffries had a test result demonstrating cold agglutinins that were indicative of an autoimmune disease. Mr. Jeffries' increased bilirubin is a by-product of red blood cell destruction, possibly secondary to an autoimmune injury to the red blood cells.

12. **CK (Creatine Kinase):**. An injury to the brain releases CK. It is my opinion that Mr. Jeffries' elevated CK is the result of either a Reye's-like syndrome, CNS injury, or hypothyroidism.

13. **RNAse L Protein.** Once again this test is substantially abnormal but is consistent with Mr. Jeffries' other tests and suggest an ongoing viral infection most likely the result of the decreased effectiveness of his immune system.

14. **Medical History.** Given Mr. Jeffries' personal and family medical history, it appears that his genetic pathology puts him in a potential increased risk of developing an autoimmune disease process. Mr. Jeffries' father suffered from two genetically inherited CNS illnesses, Usher Syndrome and Retinitis Pigmentosa, which may have left Mr. Jeffries more vulnerable to a form of CNS disease. Patients with Usher Syndrome often have a concomitant loss of intellectual ability and develop ataxia or balance problems. Mr. Jeffries is experiencing both of these problems presently. Mr. Jeffries also has one full sibling who has a significant autoimmune disease of lupus, or a lupus like disease with a positive ANA.

Mr. Jeffries' history with Rocky Mountain Spotted Fever (RMSF) may also be a factor in his present illness. The milder clinical symptoms and pathology of RMSF are similar to the symptoms and pathology that Mr. Jeffries suffers from today. It is quite possible that the original injury with RMSF from which he recovered completely has left an antibody receptor marker on the affected areas, and specifically his small arteries of the CNS and endocrine glands. and these markers have somehow been stimulated by the infection and the combined Hepatitis A & B immunization. The SPECT brain scans demonstrate a vasculitis like pattern in his brain as would be expected in a mild to moderate RMSF.

Conclusions

The incredible number of historical, clinical, and test results all are consistent with a major and overwhelming injury to the immune and CNS systems. The tests conducted on Mr. Jeffries demonstrate that he has immunological and physiological injuries consistent with his complaints and consistent with the disability that he describes. The symptoms and pattern of his illness are also consistent with both autoimmune and CNS vasculitis disease.

On the basis of the above findings and my personal observations and examinations of Mr. Jeffries, it is my opinion that Eric Jeffries is totally disabled intellectually and physically and has been so disabled since he ceased work over three years ago. Obviously, it is my opinion that he is, therefore, disabled from performing his pre-illness occupation for the present and foreseeable future. It is also my opinion that the June 1997 hepatitis immunization triggered Mr. Jeffries' complex disabling illnesses.

Yours Sincerely,

Byron Hyde, M.D.

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MERCK FROSST
Discovering today for a better tomorrow.

April 10, 2003

Dr. Byron Hyde
Ottawa, Ontario

Fax: (613) 729-0148

Dear Dr. Hyde:

SUBJECT: *RECOMBIVAX HB® - MANUFACTURING METHODS*

Your inquiry concerned methods used to produce RECOMBIVAX HB® [hepatitis B vaccine (recombinant)].

The DNA sequence that codes for the hepatitis B surface antigen (HBsAg) was originally derived from Dane particles using endogenous DNA polymerase activity. The resultant DNA was introduced into a strain of *Escherichia coli* from which a clone containing a hybrid plasmid was developed. The sequence coding for the HBsAg was identified, isolated and amplified by molecular cloning.

To manufacture RECOMBIVAX HB®, this gene was cloned into common baker's yeast, *Saccharomyces cerevisiae*. The yeast cells produce HBsAg along with their own proteins. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods which include hydrophobic interaction chromatography. The resulting purified hepatitis B surface antigen particles are treated with formaldehyde and adsorbed onto amorphous aluminum hydroxyphosphate, an adjuvant. Since May 2001, no trace of thimerosal preservative was added to any Merck pediatric vaccine formulations. The resulting product contains no human or animal material, e.g., albumin and consists of a noninfectious protein rather than a live virus.

Even though yeast-derived and plasma-derived HBsAg differ slightly in terms of physical and chemical properties, the quality of antibodies to hepatitis B surface antigen (anti-HBs) raised by the two vaccines are indistinguishable. Studies assessing the specificity, affinity and avidity of antibodies to yeast-derived and plasma-derived HBsAg are summarized by Emini EA et al. [1], and Ellis RW and Gerety RJ [2].

A more comprehensive review of the use of recombinant DNA technology in the development of RECOMBIVAX HB® was provided by Ellis RW [3].

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We trust the foregoing is of assistance and thank you for your interest.

Yours truly,

Jacques Beaudoin, Pharmacist, Ph. D.
Assistant Director
Medical Services

JB/my

(WP 9784)

REFERENCES

1. Emini EA, Ellis RW, Miller WJ, et al. Production and immunological analysis of recombinant hepatitis B vaccine.
JOURNAL OF INFECTION. 1986;13(SUPPL A): 3-11.

2. Ellis RW, Gerety RJ. Plasma-derived and yeast-derived hepatitis B vaccines.
J INFECT CONTROL. 1989;17(3): 181-189.

3. Ellis RW. Recombinant-derived hepatitis B vaccine: A paradigm for other subunit vaccines. AIDS Vaccine Research and Clinical Trials 1990: 381-407.

These are abstracts of the first two references. These abstracts come from Merck & Co.'s own database of abstracts written by Merck employees.

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Emini E A, Ellis R W, Miller W J, McAleer W J, Scolnick E M and Gerety R J
Production and Immunological Analysis of Recombinant Hepatitis B Vaccine
J Infect 13(Suppl. A): 3-11 passim, July 1986

Hepatitis B vaccine, yeast-derived (Merck), hepatitis B vaccine, plasma-derived (Merck)

The production of hepatitis B vaccine via Saccharomyces cerevisiae is described, and several studies comparing the yeast- and plasma-derived products are briefly reviewed. Both vaccines were active against the 'ad' and 'ay' HBV subtypes in chimpanzees, and they yielded virtually identical effective dose values in mice. In man, the antibodies produced in response to the yeast- and plasma-derived vaccines were equivalent in terms of development kinetics, avidity constants, cross-absorption patterns, determinant-specific (a vs d) proportions, and a-epitope binding. 8 refs.

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Ellis R W and Gerety R J
Plasma-Derived and Yeast-Derived Hepatitis-B Vaccines
Am J Infect Control 17(3): 181-189, June 1989

Plasma-derived hepatitis B vaccine, recombinant yeast-derived hepatitis B vaccine (RECOMBIVAX HB, Merck), hepatitis B virus

The development of recombinant yeast-derived hepatitis B vaccine is described and the results of studies are summarized comparing its potency and function with those of plasma-derived vaccine. In the historical development of the vaccine, improved yield and greater purification were obtained with modifications in yeast storage and growth conditions. The resulting 99% pure vaccine (antigen as a percentage of total protein) provides increased immunogenicity. However, details of the purification process vary among manufacturers, resulting in variation in immunogenicity. In vivo tests in mice documented similar levels of immunogenicity for plasma-derived and yeast-derived vaccines. Controlled studies of 3-dose regimens in chimpanzees indicated that antibodies induced by both types of vaccine were functionally equivalent, providing anti-HBs responses and protective immunity following challenge with hepatitis B virus. In vitro studies of sera from humans vaccinated with either vaccine indicated similar antibody binding capacities and affinities, similar titers of anti-e antibodies, and similar degrees of inhibition of monoclonal antibody binding. Results demonstrated that recombinant yeast-derived hepatitis B vaccine is highly immunogenic and provides the same degree of protection as the plasma-derived vaccine from hepatitis B virus. 12 refs.

PRODUCT MONOGRAPH

RECOMBIVAX HB®

[hepatitis B vaccine (recombinant)]

Injectable Solution

THERAPEUTIC CLASSIFICATION

Vaccine for immunization against infection caused by hepatitis B virus including all known subtypes

ACTION AND CLINICAL PHARMACOLOGY

Hepatitis B virus is one of at least five hepatitis viruses that cause a systemic infection, with major pathology in the liver. The others are hepatitis A, hepatitis C, hepatitis D, and hepatitis E viruses.

Hepatitis B virus is an important cause of viral hepatitis. There is no specific treatment for this disease. The incubation period for type B hepatitis is relatively long; six weeks to six months may elapse between exposure and the onset of clinical symptoms. The prognosis following infection with hepatitis B virus is variable and dependent on at least three factors: (1) Age - Infants and younger children usually experience milder initial disease than older persons;[1] (2) Dose of Virus - The higher the dose, the more likely acute icteric hepatitis B will result;[1] and, (3) Severity of Associated Underlying Disease - Underlying malignancy or pre-existing hepatic disease predisposes to increased mortality and morbidity.[1]

Persistence of viral infection (the chronic hepatitis B virus carrier state) occurs in 5-10% of persons following acute hepatitis B, and occurs more frequently after initial anicteric hepatitis B than after initial icteric disease. Consequently, carriers of hepatitis B surface antigen (HBsAg) frequently give no history of recognized acute hepatitis. The World Health Organization estimated that more than 2 billion people worldwide have evidence of post or current hepatitis B virus infection, and 350 million are chronic carriers of the virus.[2] The Centers for Disease Control (CDC) estimate that there are approximately 0.5 to 1.0 million chronic carriers of hepatitis B virus in the USA and that this pool of carriers grows by 2-3% (8000 to 16,000 individuals) annually.[3] Chronic carriers represent the largest human reservoir of hepatitis B virus.

The serious complications and sequelae of hepatitis B virus infection include massive hepatic necrosis, cirrhosis of the liver, chronic active hepatitis, and hepatocellular carcinoma.[4] Chronic carriers of HBsAg appear to be at increased risk of developing hepatocellular carcinoma, which accounts for 80 to 90% of primary liver carcinomas.[5] Although a number of etiologic factors are associated with development of hepatocellular carcinoma, the single most important etiologic factor appears to be active infection with the hepatitis B virus.[2] Globally, approximately one million individuals die each year as a direct result of HBV-induced cirrhosis or liver cancer.[6] Based on death certificates, about 100 Canadians died in 1995 due to hepatitis B associated acute or chronic liver disease.[7]

There is also evidence that several diseases other than hepatitis have been associated with hepatitis B virus infection through an immunologic mechanism involving antigen-antibody complexes. Such diseases include a syndrome with rash, urticaria and arthralgia resembling serum sickness; polyarteritis nodosa; membranous glomerulonephritis; and infantile papular acrodermatitis.[2]

Although the vehicles for transmission of the virus are predominantly blood and blood products, viral antigen has also been found in tears, saliva, breast milk, urine, semen and vaginal secretions. Hepatitis B virus is capable of surviving for days on environmental surfaces. Infection may occur when hepatitis B virus, transmitted by infected body fluids, is implanted via mucous surfaces or percutaneously introduced through accidental or deliberate breaks in the skin.

Transmission of hepatitis B virus infection is often associated with close interpersonal contact with an infected individual and with crowded living conditions. In such circumstances, transmission by inoculation via routes other than overt parenteral ones may be quite common.[8] Perinatal transmission of hepatitis B infection from infected mother to child, at, or shortly after birth, can occur if the mother is an HBsAg carrier or if the mother has an acute hepatitis B infection in the third trimester.[9] Infection in infancy by the hepatitis B virus usually leads to the chronic carrier state. Among infants born to women whose sera are positive for both the hepatitis B surface antigen and the e antigen, 85-90% are infected and become chronic carriers.[9,10]

Hepatitis B is endemic throughout the world, and is a serious medical problem in population groups at increased risk (see INDICATIONS AND CLINICAL USE). The prevalence of HBsAg in the general population varies between less than 0.5% in the U.S., Canada and Western Europe, 1 to 2% in South America and Southern Europe, 3 to 5% in North Africa and in many parts of the Federation of Russia (formally known as USSR) and 9 to 10% and higher in sub-Saharan Africa, Southeast Asia and Alaska.[11,12] The overall prevalence of serologic markers of infection varies between 7 and 10% in the U.S. and 60 and 80% in Southeast Asia or Africa.[11] Even in countries like those in Northern and Western Europe and other highly developed countries with a relatively low prevalence of hepatitis B, certain populations are at high risk of acquiring the disease and have cumulative infection rates of up to 70% (see INDICATIONS AND CLINICAL USE).[11] In countries or areas with a high prevalence rate, the entire population is at risk and infection tends to occur during childhood.

Numerous epidemiological studies have shown that persons who develop anti-HBs following active infection with the hepatitis B virus are protected against the disease on re-exposure to the virus.

Reports in the literature describe a more virulent form of hepatitis B associated with superinfections or coinfections by delta virus, an incomplete RNA virus. Delta virus can only infect and cause illness in persons infected with hepatitis B virus since the delta agent requires a coat of HBsAg in order to become infectious. Therefore, persons immune to hepatitis B virus infection should also be immune to delta virus infection.[13,14]

Clinical Studies

Clinical studies have established that RECOMBIVAX HB® [hepatitis B vaccine (recombinant)], when injected into the deltoid muscle, induced protective levels of antibody in greater than 90% of healthy individuals who received the recommended 3-dose regimen. Studies with hepatitis B vaccine derived from plasma have shown that a lower response rate (81%) to vaccine may be obtained if the vaccine is administered as a buttock injection.[15] A protective antibody (anti-HBs) level has been defined as 10 or more sample ratio units (SRU) as determined by radioimmunoassay or a positive by enzyme immunoassay.[16]

Responsiveness to the vaccine was age dependent. The seroprotection rate for children 1-10 years of age and adolescents 11-15 years of age were 100% and 99%, respectively. In contrast, the seroprotection rate for adults ranged from 95 to 98% for those from 20 to 39 years of age and 91% for those of 40 years of age or older.

The protective efficacy of three 5 µg doses of RECOMBIVAX HB® has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg. In a clinical study of infants who received one dose of Hepatitis B Immune Globulin at birth followed by the recommended three-dose regimen of RECOMBIVAX HB®, efficacy in prevention of chronic hepatitis B infection was 96% in 47 infants at six months and 100% in 19 infants at nine months.

For adolescents (11 to 15 years of age), the immunogenicity of a two-dose regimen (10 µg at 0 and 4-6 months) was compared with that of the standard three-dose regimen (5 µg at 0, 1 and 6 months) in an open, randomized, multicenter study. The proportion of adolescents receiving the two-dose regimen who developed a protective level of antibody one month after the last dose (99% of 255 subjects) appears similar to that among adolescents who received the three-dose regimen (98% of 121 subjects). After adolescents (11 to 15 years of age) received the first 10 µg dose of the two-dose regimen, the proportion who developed a protective level of antibody was approximately 72%.

Predialysis and Dialysis Patients

Immunocompromised persons respond less well to RECOMBIVAX HB® than do healthy individuals. Vaccine-induced levels of anti-HBs are lower in pre-dialysis and hemodialysis patients than are the levels in healthy individuals. Eighty-six percent (86%) of pre-dialysis and hemodialysis patients who received three 40 µg doses of RECOMBIVAX HB® developed protective levels of anti-HBs.

Duration of Protection

As with other hepatitis B vaccines, the duration of protective effect of RECOMBIVAX HB® is unknown at present, and the need for booster doses not defined. However, long-term follow-up (5 to 9 years) of approximately 3000 high-risk vaccinees (infants of carrier mothers, male homosexuals, Alaskan Natives) who developed an anti-HBs titer of ≥ 10 mIU/mL when given a similar plasma-derived vaccine at intervals of 0, 1, and 6 months showed that no subjects developed clinically apparent hepatitis B infection and that 5 subjects developed antigenemia, even though up to half of the subjects failed to maintain a titer at this level.[17-19] Persistence of vaccine-induced immunologic memory among healthy vaccinees who responded to a primary course of plasma-derived or recombinant hepatitis B vaccine has been demonstrated by an anamnestic antibody response to a booster dose of RECOMBIVAX HB® given 5-12 years later.[21]

Routine booster vaccinations in immunocompetent persons are not recommended since protection has been shown to last for at least 15 years. Studies of long-term protective efficacy, however, will determine whether booster doses of vaccine are ever needed. It is important to recognize that absence of detectable anti-HBs in a person who has been previously demonstrated to have anti-HBs does not mean lack of protection, because immune memory persists. Booster doses in this situation are not indicated.[22]

Immunocompromised persons often respond suboptimally to the vaccine. Subsequent HBV exposures in these individuals can result in disease or the carrier state. Therefore, boosters may be necessary in this population. The optimal timing of booster doses for immunocompromised individuals who are at continued risk of HBV exposure is not known and should be based on the severity of the compromised state and annual monitoring for the presence of anti-HBs.[22]

Post-Exposure

Studies have established the relative efficacies of immune globulin and/or hepatitis B vaccine in accidental percutaneous or permucosal exposure to HBsAg-positive blood; or sexual exposure to HBsAg-positive persons (see DOSAGE AND ADMINISTRATION).

It has been demonstrated that doses of up to 5 mL of Hepatitis B Immune Globulin, when administered simultaneously with the first dose of RECOMBIVAX HB® at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the three-dose vaccine regimen.

Interchangeability

Hepatitis B vaccines produced by different manufacturers can be used interchangeably despite different doses and schedules. The dose used should be that recommended by the manufacturer.[23]

INDICATIONS AND CLINICAL USE

RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

RECOMBIVAX HB® will not prevent hepatitis caused by other agents, such as hepatitis A virus, non-A, non-B hepatitis viruses, or other viruses known to infect the liver.

Vaccination with RECOMBIVAX HB® is recommended in persons of all ages, especially those who are or will be at increased risk of infection with hepatitis B virus. In areas with low prevalence like Canada, universal immunization before adolescence is recommended.[23] Special efforts should also target the high-risk populations.[23]

A. **Infants Born to HBsAg-Positive Mothers**

B. **Children < 7 years of age whose families have immigrated** to Canada from areas where there is a high prevalence of hepatitis B, and who are exposed to hepatitis B virus carriers through their extended families.

C. **Adolescents** (see ACTION AND CLINICAL PHARMACOLOGY)

D. **Health-Care Personnel**

Dentists and oral surgeons
Physicians and surgeons
Nurses
Paramedical personnel and custodial staff who may be exposed to the virus via blood or other patient specimens (i.e., body fluids and tissues)
Dental hygienists and dental nurses
Laboratory personnel handling blood, blood products and other patient specimens (i.e., body fluids and tissues)
Dental, medical and nursing students, preferably soon after acceptance in the university

E. **Selected Patients and Patient Contacts**

Patients and staff in hemodialysis units and hematology/oncology units
Patients requiring frequent and/or large-volume blood transfusions or clotting factor concentrates (e.g., persons with hemophilia, thalassemia)
Patients (residents) and staff of institutions for the mentally handicapped
Classroom contacts of deinstitutionalized mentally handicapped persons who have persistent hepatitis B antigenemia and who show aggressive behavior
Household and other intimate contacts of persons with persistent hepatitis B antigenemia
Children in child-care settings in which there is a hepatitis B virus-infected child. These children should receive serious consideration for immunization against hepatitis B virus.

F. **Travellers to Hepatitis B Endemic Areas**

G. **Military Personnel identified as Being at Increased Risk**

H. **Emergency Service Workers (police, firefighters)**

I. **Morticians and Embalmers**

J. **Blood Bank and Plasma Fractionation Workers**

K. **Persons at Increased Risk of the Disease Due to Their Sexual Practices[1]** such as:

Persons who have heterosexual activity with multiple partners
Persons who repeatedly contract sexually transmitted diseases
Homosexually active males
Female prostitutes

L. **Prisoners**

M. **Users of Illicit Injectable Drugs**

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

WARNINGS

Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is given. RECOMBIVAX HB® may not prevent hepatitis B in such patients.

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of RECOMBIVAX HB® (see CONTRAINDICATIONS).

PRECAUTIONS

General

Persons with immunodeficiency or those receiving immunosuppressive therapy require larger vaccine doses and respond less well than healthy individuals.

As with any parenteral vaccine, epinephrine should be available for immediate use should an anaphylactoid reaction occur.

Any serious active infection is reason for delaying use of RECOMBIVAX HB® [hepatitis B vaccine (recombinant)], except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Caution and appropriate care should be exercised in administering RECOMBIVAX HB® to individuals with severely compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

Pregnancy

Animal reproduction studies have not been conducted with RECOMBIVAX HB®. It is also not known whether RECOMBIVAX HB® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. RECOMBIVAX HB® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether RECOMBIVAX HB® is excreted in human milk. However, studies with RECOMBIVAX HB® in 12 lactating women have failed to reveal evidence of this vaccine being secreted.

Pediatric Use

RECOMBIVAX HB® has been shown to be generally well tolerated and highly immunogenic in infants and children of all ages. Newborns have responded well; maternally transferred antibodies did not interfere with the active immune response to the vaccine. See DOSAGE AND ADMINISTRATION for recommended pediatric dosage and recommended dosage for infants born to HBsAg-positive mothers. The safety profile and effectiveness of the dialysis formulation in children have not been established.

ADVERSE REACTIONS

RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is generally well tolerated. No serious adverse reactions attributable to vaccination were reported during the course of clinical trials involving administration of RECOMBIVAX HB® to over 1000 individuals. The frequency of complaints was somewhat lower following the second and third vaccine doses compared with the first dose. As with any vaccine, there is the possibility that broad use of the vaccine could reveal rare adverse reactions not observed in clinical trials.

No adverse reactions were reported during clinical trials which could be related to yeast.

In a study that compared the three-dose regimen (5 µg) with the two-dose regimen (10 µg) of RECOMBIVAX HB® in adolescents, the overall frequency of adverse reactions was generally similar.

In a group of studies 3258 doses of RECOMBIVAX HB® were administered to 1252 healthy adults. Vaccine recipients were monitored for 5 days after each dose, and the following adverse reactions were reported:

	% of Doses
Local Reactions in Injection Site	
Injection site reactions, consisting principally of local pain, soreness and tenderness and including pruritus, erythema, ecchymoses, swelling, warmth and nodule formation.	16.7%
Body as a Whole	
Fatigue/asthenia	4.2%
Malaise	1.2%
Fever ≥ 37.8°C	3.2%
Sweating	0.5%
Chills	0.2%
Flushing	0.2%
Aching	0.4%
Sensation of warmth	0.4%
Digestive System	
Nausea	1.8%
Diarrhea	1.1%
Vomiting	0.3%
Abdominal pains/cramps	0.3%
Dyspepsia	0.2%
Diminished appetite	0.1%
Integumentary System	
Pruritus	0.3%
Rash	0.2%
Urticaria	0.1%
Musculoskeletal System	
Myalgia	0.4%
Arthralgia	0.5%
Back pain	0.2%
Neck pain	0.2%
Shoulder pain	0.2%
Neck stiffness	0.2%
Nervous System	
Headache	4.1%
Light headedness	0.3%
Vertigo/dizziness	0.5%
Paresthesia	0.1%
Respiratory System	
Pharyngitis	1.2%
Rhinitis	0.8%
Cough	0.2%
Upper respiratory infection (NOS)	1.0%
Influenza	0.3%
Special Senses	
Earache	0.2%

Other Incidences Reported in Less than 1% of Injections

Cardiovascular System

Hypotension

Hemic/Lymphatic System

Lymphadenopathy

Integumentary System

Angioedema

Psychiatric/Behavioral

Insomnia/disturbed sleep

Urogenital System

Dysuria

POST-MARKETING EXPERIENCE

The following additional adverse reactions have been reported with use of the marketed vaccine; however, in many instances a causal relationship to the vaccine has not been established.

Hematologic

Increased erythrocyte sedimentation rate.

Hypersensitivity

Anaphylaxis and symptoms of immediate hypersensitivity reactions including edema, dyspnea, chest discomfort, bronchial spasm, or palpitation have been reported within the first few hours after vaccination. An apparent hypersensitivity syndrome (serum-sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthritis (usually transient), and dermatologic reactions such as erythema multiforme, ecchymoses and erythema nodosum (see PRECAUTIONS).

Nervous System

Peripheral neuropathy including Bell's Palsy; Guillain-Barré syndrome; optic neuritis; exacerbation of multiple sclerosis, *multiple sclerosis; seizure and febrile seizure; encephalitis.*

Immune System

Vasculitis

Musculoskeletal System

Arthritis

Integumentary System

Alopecia

Special Senses

Tinnitus

DOSAGE AND ADMINISTRATION

The deltoid muscle is the preferred site for intramuscular injection in adults. The anterolateral thigh is the recommended site for intramuscular injection in infants and children. Data suggest that injections given in the buttocks are given frequently into fatty tissue instead of into muscle. Such injections may result in a lower seroconversion rate than is expected.[16]

The vaccine should be used as supplied. No dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

It is recommended to record lot numbers when the vaccine is administered to a recipient.

FOR INTRAMUSCULAR USE

Do not inject intravenously or intradermally.

RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is for intramuscular injection. It may, however, be administered subcutaneously to persons at risk of hemorrhage following intramuscular injections. However, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons (e.g., hemophiliacs) at risk of hemorrhage following intramuscular injections.

Shake well before withdrawal and use.

Thorough agitation at the time of administration is necessary to maintain suspension of the vaccine. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. After thorough agitation, RECOMBIVAX HB® is a slightly opaque, white suspension.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another.

For the preservative-free (thimerosal-free) formulations: Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Three-Dose Regimen

The vaccination regimen consists of three doses of vaccine given according to the following schedule:

First injection:	at elected date
Second injection:	≥ 1 month after first injection
Third injection:	≥ 1 month after second injection

Within limits, the timing of successive injections may be adjusted to accommodate a variety of needs, such as coadministration with other vaccines.

For infants born of mothers who are HBsAg positive or mothers of unknown HBsAg status, treatment recommendations are described in the subsections titled: **Dosage for Infants Born to HBsAg-positive Mothers.**

A minimum of one month should separate successive injections of vaccine. Accelerated three-dose regimens (e.g., 0, 1, 2 months; 0, 2, 4 months) may induce protective antibody earlier in a slightly larger proportion of vaccinees. However, regimens that extend the time interval between the second and third injections (e.g., 0, 1, 6 months; 0, 1, 12 months) will ultimately seroconvert a similar proportion of vaccinees while inducing substantially higher antibody titers than accelerated regimens.

The dose of vaccine to be given on each occasion is as follows:

GROUP	REGIMEN
INFANTS*/CHILDREN (birth to 10 years of age)	3 x 2.5 µg
ADOLESCENTS (11-19 years of age)	3 x 5 µg
ADULTS (≥ 20 years)	3 x 10 µg

*Infants born of HBsAg-negative mothers.

Two-Dose Regimen - Adolescents (11 to 15 years of age)

An alternate two-dose regimen is available for routine vaccination of adolescents (11 to 15 years of age). The regimen consists of two doses of vaccine (10 µg) given according to the following schedule:

1st dose:	at elected date
2nd dose:	4 to 6 months after the first dose

GROUP	INITIAL	4-6 MONTHS
ADOLESCENTS** (11-15 years of age)	10 µg	10 µg

**Adolescent (11 to 15 years of age) may receive either regimen, the 3 X 5 µg or the 2 X 10 µg (see DOSAGE AND ADMINISTRATION, Three-Dose and Two-Dose Regimens).

RECOMBIVAX HB® Dialysis 40 µg/mL Formulation

RECOMBIVAX HB® DIALYSIS FORMULATION (40 µg/mL) IS INTENDED ONLY FOR ADULT PREDIALYSIS/DIALYSIS PATIENTS.

The recommended vaccination regimen for predialysis/dialysis patients is as follows:

GROUP	INITIAL	1 MONTH	6 MONTHS
PREDIALYSIS/DIALYSIS Adult dialysis presentation 40 µg/1.0 mL	40 µg	40 µg	40 µg

RECOMBIVAX HB® preservative-free (thimerosal-free) Formulations

RECOMBIVAX HB® preservative-free formulations are available for use in individuals for whom a thimerosal-free vaccine may be desired. These formulations are intended for single-use only.

Revaccination of Nonresponders

When persons who do not respond (anti-HBs < 10 IU/l) to the primary vaccine series are revaccinated, 15-25% produce an adequate antibody response after one additional dose and 30-50% after three additional doses.[23,24] However, because data are insufficient concerning the safety of hepatitis B vaccine when additional doses in excess of the recommended two- or three-dose series are administered, revaccination following completion of the primary series is not routinely recommended. Revaccination should only be considered for high-risk individuals, after weighing the benefits of vaccination against the potential risk of experiencing increased local or systemic adverse reactions.

Dosage for Infants Born to HBsAg-positive Mothers

Infants born to HBsAg-positive mothers are at high risk of becoming chronic carriers of hepatitis B virus and of developing the chronic sequelae of hepatitis B virus infection. Well controlled studies have shown that administration of three 0.5 mL doses of hepatitis B immune globulin starting at birth is 75% effective in preventing establishment of the chronic carrier state in these infants during the first year of life.[14] Protection is transient under these circumstances and the effectiveness of the passively administered hepatitis B immune globulin declines thereafter. Results from clinical studies indicate that administration of one 0.5 mL dose of hepatitis B immune globulin at birth and three 5 µg (0.5 mL) doses of RECOMBIVAX HB®, the first dose given within one week after birth, was 98% effective in preventing establishment of the chronic carrier state in infants born to HBsAg- and HBeAg-positive mothers. Testing for HBsAg and anti-HBs is recommended at 12-15 months to monitor the final success or failure of therapy. If HBsAg is not detectable, and anti-HBs is present, the child has been protected.

The recommended dosage for infants born to HBsAg-positive mothers is as follows:

TREATMENT	BIRTH	1 MONTH	6 MONTHS
RECOMBIVAX HB®	5 µg***	5 µg	5 µg
Hepatitis B immune globulin	0.5 mL		

***The first dose of RECOMBIVAX HB® (5 µg) may be given at birth at the same time as hepatitis B immune globulin, but should be administered in the opposite anterolateral thigh. This procedure may be preferable to ensure absorption of the vaccine.

Acute Exposure to Blood Containing HBsAg

There are no prospective studies directly testing the efficacy of a combination of hepatitis B immune globulin and RECOMBIVAX HB® in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, recent studies have established the relative efficacies of immune globulins and/or hepatitis B vaccine in various exposure situations. Since most persons with such exposures (e.g., health-care workers) are candidates for the hepatitis B vaccine and since combined hepatitis B immune globulin plus vaccine is more efficacious than hepatitis B immune globulin alone in perinatal exposures, the following guidelines are recommended for persons who have been exposed to hepatitis B virus such as through (1) percutaneous (needlestick), ocular, mucous membrane exposure to blood known or presumed to contain HBsAg, (2) human bites by known or presumed HBsAg carriers, that penetrate the skin, or (3) following intimate sexual contact with known or presumed HBsAg carriers:

Hepatitis B immune globulin (0.06 mL/kg) should be given as soon as possible after exposure and within 24 hours if possible. Hepatitis B vaccine should be given intramuscularly within 7 days of exposure and second and third doses given one and six months, respectively, after the first dose.

For Syringe Use Only: Withdraw the recommended dose from the vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

PHARMACEUTICAL INFORMATION

DESCRIPTION

RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is a non-infectious subunit viral vaccine consisting of surface antigen (HBsAg or Australia antigen) of hepatitis B virus produced in yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The currently produced vaccine contains no detectable yeast DNA but may contain <1% yeast protein. The vaccine produced by the Merck method has been shown to be comparable to the plasma-derived vaccine in terms of protective efficacy (chimpanzee and human).

The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

Each lot of hepatitis B vaccine is tested for safety, in mice and guinea pigs, and for sterility.

COMPOSITION

RECOMBIVAX HB® is a sterile suspension for intramuscular injection; however, it may be administered subcutaneously to persons at risk of hemorrhage following intramuscular injections (see DOSAGE AND ADMINISTRATION).

Two formulations are available:

- 10 µg/1.0 mL formulation: each 1.0 mL dose contains 10 µg of hepatitis B surface antigen adsorbed onto approximately 0.5 mg of amorphous aluminum hydroxyphosphate;
- 40 µg/1.0 mL formulation: each 1.0 mL dose contains 40 µg of hepatitis B surface antigen adsorbed onto approximately 0.5 mg of amorphous aluminum hydroxyphosphate;

Thimerosal (mercury derivative) 1:20,000 (50 µg/mL) has been added only to the preservative-containing formulations.

All preparations have been treated with formaldehyde prior to adsorption onto amorphous aluminum hydroxyphosphate. The vaccine is of the *adw* subtype.

STABILITY AND STORAGE RECOMMENDATIONS

Store unopened and opened vials at 2°C - 8°C. Storage above or below the recommended temperature may reduce potency.

Do not freeze because freezing destroys potency.

The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Do not use vaccine after the expiration date.

AVAILABILITY OF DOSAGE FORMS

Preservative-containing (thimerosal) Formulations

10 µg/1.0 mL formulation:

- 1.0 mL vial containing 10 µg of antigen (adult presentation)
- 3.0 mL vial containing 30 µg of antigen (adult presentation)

Preservative-free (thimerosal-free) Formulations

10 µg/1.0 mL formulation:

- 0.5 mL vial containing 5 µg of antigen (pediatric presentation)

40 µg/1.0 mL formulation:

- 1.0 mL vial containing 40 µg of antigen (adult dialysis presentation)

REFERENCES

1. Robinson WS. Hepatitis B Virus and Hepatitis Delta Virus. In: Principles and Practice of Infectious Diseases. Mandell GL, Douglas RG, and Bennett JE, eds. Churchill Livingstone, 1990;1204-31.
2. World Health Organization. The World Health Report 1998. Life in the 21st Century - A vision for all. Executive Summary, 1998;11.
3. Recommendation of the Immunization Practices Advisory Committee (ACIP). Protection against viral hepatitis. MMWR 1990;39(RR-2):5-22.
4. Dienstag JL, Wands JR, Koff RS. Acute Hepatitis. In: Harrison's Principles of Internal Medicine. Ed. 9. Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG, Wilson JD, eds. New York, McGraw-Hill, 1980;1459-70.
5. Alpert E, Isselbacher KJ. Tumors of the Liver. In: Harrison's Principles of Internal Medicine. Ed. 9. Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG, Wilson JD, eds. New York, McGraw-Hill, 1980;1484-6.
6. World Health Organization. Hepatitis B Vaccine. Making global progress 1998.
7. Annual Morbidity Report, Statistics Canada 1995.
8. Szmuness W, Much MI, Prince AM, Hoofnagle JH, Cherubin CE, Harley EJ, Block GH. On the Role of Sexual Behavior in the Spread of Hepatitis B Infection. Ann Intern Med 1975;83(4):489-95.
9. Stevens CE, Toy PT, Tong MJ, Taylor PE, Vyas GN, Nair PV, Gudavalli M, Krugman S. Perinatal Hepatitis B Virus Transmission in the United States. JAMA 1985;253(12):1740-5.
10. Beasley RP, Hwang LY, Stevens CE, Lin CC, Hsieh FJ, Wang KY, Sun TS, Szmuness W. Efficacy of Hepatitis B Immune Globulin for Prevention of Perinatal Transmission of the Hepatitis B Virus Carrier State. Final Report of a Randomized Double-Blind, Placebo-Controlled Trial. Hepatology 1983;3(2):135-41.
11. Szmuness W, Harley EJ, Ikram H, Stevens CE. Socio-demographic Aspects of the Epidemiology of Hepatitis B. In: The Franklin Inst Press. Vyas GN, Cohen SN, Schmid R, eds. Philadelphia, 1978;297-320.
12. World Health Organization. Geographic Pattern of Hepatitis B Prevalence, 1997.
13. Hadler SC, De Monzon M, Ponzetto A, Anzola E, Rivero D, Mondolfi A, Bracho A, Francis DP, Gerber MA, Thung S, Gerin J, Maynard JE, Popper H, Purcell H. Delta Virus Infection and Severe Hepatitis. Ann Intern Med 1984;100(3):339-44.
14. Redeker AG. Delta Agent and Hepatitis B. Ann Intern Med 1983;98(4):542-3.
15. Centers for Disease Control. Suboptimal Response to Hepatitis B Vaccine given by Injection into the Buttock. MMWR 1985;34(8):105-13.
16. Centers for Disease Control. Recommendations for Protection against Viral Hepatitis. MMWR 1985;34(22):313-35.
17. Wainwright RB, McMahon BJ, Bulkow LR, Parkinson AJ, Harpster AP, Hadler SC. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population, preliminary results of an 8-year study. In: Viral Hepatitis and Liver Disease. Hollinger FB, Lemon SM and Margolis H, eds. Williams & Wilkins 1990;762-6.
18. Hadler SC, Coleman PJ, O'Malley P, Judson FN, Altman N. Evaluation of long-term protection by hepatitis B vaccine for seven to nine years in homosexual men. In: Viral Hepatitis and Liver Disease. Hollinger FB, Lemon SM and Margolis H, eds. Williams & Wilkins 1990;766-8.
19. Tong MJ, Stevens CE, Taylor PE, Toy PT, Vyas G, Krugman S. Prevention of hepatitis B infection in infants born to HbeAg positive HbsAg carrier mothers in the United States. An Update, 1989, Progress in Hepatitis B Immunization. Coursaget P and Tong MJ, eds. Colloque INSERM/John Libbey Eurotext Ltd. 1990;194:339-45.
20. Hwang LY, Lee CY, and Beasley RP. Five-year follow-up of HBV vaccination with plasma-derived vaccine in neonates: Evaluation of immunogenicity and efficacy against perinatal transmission. In: Viral Hepatitis and Liver Disease. Hollinger FB, Lemon SM and Margolis H, eds. Williams & Wilkins 1990;758-61.
21. West DJ, Calandra GB. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. Vaccine 1996;14(11):1019-27.
22. National Advisory Committee on Immunization (NACI). Hepatitis B Vaccine. In: Canadian Immunization Guide, Fifth Edition. Published by Authority of the Minister of Health and in collaboration with the Canadian Medical Association, Ottawa, Canada. 1998:90-102.
23. MMWR, 40(RR-13), November 22, 1991.
24. Hadler SC et al. Long-Term Immunogenitiy and Efficacy of Hepatitis B Vaccine in Homosexual Men. N Engl J Med July 24, 1986;314(4):209-14.

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